BASIC RESEARCH ON BIOMECHANICAL SIGNALING MECHANISMS IN CARTILAGE

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RFA: AR-98-005

P.T.

National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute on Aging

Letter of Intent Receipt Date: March 15, 1998
Application Receipt Date: April 28, 1998

PURPOSE

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and the National Institute on Aging (NIA) invite applications for basic research on mechanisms of biomechanical signaling in cartilage. The applications may be for individual research projects or for a group of independent research projects that use the interactive research project grant (IRPG) mechanism. The research should be specifically targeted towards understanding the signal transduction and regulatory pathways through which articular cartilage chondrocytes sense and respond to mechanical stimuli. This Request for Applications (RFA) requests basic and applied research projects, but not epidemiological or clinical treatment projects.

HEALTHY PEOPLE 2000

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2000," a PHS-led national activity for setting priority areas. This RFA, Basic Research on Biomechanical Signaling Mechanisms in Cartilage, is related to the priority areas of chronic disabling conditions and of older adults and preventive services. Potential applicants may obtain a copy of "Healthy People 2000" (Full Report: Stock No. 017-001-00474-0 or Summary Report: Stock No. 017-001-00473-1) through the Superintendent of Documents, Government Printing Office, Washington, DC 20402-9325 (telephone 202-512-1800).

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic and foreign for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as Principal Investigators.

MECHANISM OF SUPPORT

This RFA will use the National Institutes of Health (NIH) individual research grant (R01) and interactive research project grants (IRPG) mechanisms. The IRPG mechanism encourages interaction and collaboration among independent scientists with common goals. It is intended to bring together research projects from investigators who wish to collaborate but who do not require extensive shared resources. There should be constructive interchange of ideas, data and/or materials. A minimum of two independent investigators are encouraged to submit concurrent, collaborative, cross-referenced individual regular research project grant (R01) applications. These applications must be free-standing and contain independent hypotheses and aims. An application that provides only a service to other applicants is not acceptable.
Applicants may be from one or several institutions. Potential applicants contemplating the submission of an IRPG should contact the program official listed under INQUIRIES at an early opportunity. Guidelines for preparing IRPG applications are available from the program official or from the internet at: http://grants.nih.gov/grants/funding/irpg.htm.

Responsibility for the planning, direction, and execution of the proposed project will be solely that of the applicant. The anticipated award date is September 30, 1998. Because the nature and scope of the research proposed in response to this RFA may vary, it is anticipated that the size of an award will also vary. This RFA is a one time solicitation. Future unsolicited competing continuation applications will compete with all investigator initiated applications and be reviewed according to customary peer review procedures.

Applicants from institutions that have a General Clinical Research Center (GCRC) funded by the NIH National Center for Research Resources may wish to identify the GCRC as a resource for conducting the proposed research. If so, a letter of agreement from either the GCRC Program Director or Principal Investigator should be included within the application.

FUNDS AVAILABLE

It is anticipated that six to eight awards will be made as a result of applications for "Basic Research on Biomechanical Signaling Mechanisms in Cartilage." The estimated funds available for the first year of support for the program are $1,250,000 dollars. Actual funding is contingent upon receipt of a sufficient number of scientifically meritorious applications. Funding beyond the first and subsequent years of the grant will be contingent upon satisfactory progress during the preceding years and the availability of funds.

RESEARCH OBJECTIVES

The purpose of this RFA is to stimulate basic research in mechanisms of biomechanical signaling in cartilage. Mechanical loading of articular cartilage is required for normal growth and maintenance of the tissue, and anomalous mechanical loading of the tissue can lead to joint damage. Clinical and experimental evidence indicates that removal of mechanical stimulation by immobilization of a joint leads to suppression of matrix synthesis, degradation of matrix components, and decreased growth. Destabilization of the knee, leading to abnormal loading conditions, may result in the development of osteoarthritis. The molecular mechanisms underlying these and other mechanical effects are not well understood.

Recent progress in cell biology has delineated the importance of signaling factors in controlling cellular functions and promoting cell survival for a variety of cell types, but less is known about signaling pathways in chondrocytes. The roles of various different stimuli such as hydrostatic pressure, membrane stretching, and fluid shear in the transduction of mechanical forces into cellular activities remain unresolved. Chondrocytes, like other cells, exist in an information-rich environment containing extracellular matrix macromolecules, cytokines, hormones, and remodeling enzymes. Transmembrane receptors detect and relay extracellular signals to intracellular responsive elements and subsequently influence gene expression. Identification of cellular and molecular signaling mechanisms in cartilage and their roles in normal and abnormal joints may not only provide key information on the pathogenesis of osteoarthritis, but also may open new sites for potential therapeutic intervention. Appropriate research areas may include, but are not limited to, the following:

o Development of in vivo or in vitro systems that will allow analysis of cellular responses to biomechanical stimuli;

o Elucidation of biomechanical signal transduction pathways in chondrocytes;

o Studies on mechanical regulation of the structure/function of the cartilage matrix;

o Studies on the role of mechanical influences on the degradation and repair of cartilage at the cellular level;

o Analysis of biomechanical effects on chondrocyte metabolic activities, responses to cytokines, gene expression and changes in osteoarthritis;

o Age-related changes in cellular response to biomechanical stimuli, including changes in turnover of cartilage, the signal transduction pathway, and gene expression; and, effects of age-related changes in joint anatomy or cartilage composition on biomechanical signaling.

This list is intended to be illustrative and not exclusive or restrictive.
Applications combining interdisciplinary approaches that include collaborations between biomechanical engineers and cell biologists are strongly encouraged. Integration of mechanisms across a range of events such as joint loading to molecular events at the cell membrane and gene expression levels are also highly recommended.

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their subpopulations must be included in all NIH supported biomedical and behavioral research projects involving human subjects so that research findings can be of benefit to all persons at risk of the disease, disorder or condition under study. If women or minorities are excluded or inadequately represented a clear compelling rationale must be provided. All investigators proposing research involving human subjects should read the "NIH Guidelines For Inclusion of Women and Minorities as Subjects in Clinical Research," which have been published in the Federal Register of March 28, 1994 (FR 59 14508-14513) and in the NIH Guide for Grants and Contracts, Volume 23, Number 11, March 18, 1994. This information is available on the internet at http://grants.nih.gov/grants/guide/notice-files/not94-100.html.

Investigators also may obtain copies of the policy from the program staff listed under INQUIRIES. Program staff may also provide additional relevant information concerning the policy.

LETTER OF INTENT

Prospective applicants are asked to submit, by March 15, 1998, a letter of intent that includes a descriptive title of the proposed research, the name, address, and telephone number of the

Principal Investigator, the identities of other key personnel and participating institutions, and the number and title of the RFA in response to which the application may be submitted.

Although a letter of intent is not required, is not binding, and does not enter into the review of subsequent applications, the information that it contains allows NIAMS staff to estimate the potential review workload and to avoid conflict of interest in the review.

The letter of intent is to be sent to:

Tommy L. Broadwater, Ph.D.
Scientific Review Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
45 Center Drive, Room 5AS-25U, MSC 6500
Bethesda, MD 20892-6500
Telephone: (301) 594-4952
FAX: (301) 480-4543
Email: broadwater@nih.gov

APPLICATION PROCEDURES

The research grant application form PHS 398 (rev. 5/95) is to be used in applying for these grants. These forms are available at most institutional offices of sponsored research and from the Division of Extramural Outreach and Information Resources, National Institutes of Health, 6701 Rockledge Drive, MSC 7910, Bethesda, MD 20892-7910, telephone 301/435-0714, email:asknih@od.nih.gov
.

The RFA label available in the PHS 398 (rev. 5/95) application form must be affixed to the bottom of the face page of the application. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the RFA title and number must be typed on line 2 of the face page of the application form and the YES box must be marked.

Submit a signed original of the application, including the Checklist, and three signed copies in one package to:

CENTER FOR SCIENTIFIC REVIEW (formerly Division of Research Grants)

NATIONAL INSTITUTES OF HEALTH
6701 ROCKLEDGE DRIVE, ROOM 1040 - MSC-7710
BETHESDA, MD 20892-7710
BETHESDA, MD 20817 (for express/courier service)

At the time of submission, two additional copies of the application must also be sent to:

Tommy L. Broadwater, Ph.D.
Scientific Review Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
45 Center Drive, Room 5AS-25U, MSC 6500
Bethesda, MD 20892-6500
Telephone: (301) 594-4952
FAX: (301) 480-4543
Email: broadwater@nih.gov

Applications must be received by April 28, 1998. If an application is received after that date, it will be returned to the applicant without review. The Center for Scientific Review (CSR) will not accept any application in response to this RFA that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. The CSR will not accept any application that is essentially the same as one already reviewed. This does not preclude the submission of substantial revisions of applications already reviewed, but such applications must include an introduction addressing the previous critique.

REVIEW CONSIDERATIONS

Upon receipt, applications will be reviewed for completeness by CSR and responsiveness by the NIAMS and NIA staff. Incomplete applications will be returned to the applicant without further consideration. If the application is not responsive to the RFA, NIAMS staff will contact the applicant to determine whether to return the application to the applicant or submit it for review in competition with unsolicited applications at the next review cycle.

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened in accordance with the standard NIH peer review procedures. As part of the initial merit review, all applications will receive a written critique and undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed,

assigned a priority score, and receive a second level review by the National Arthritis and Musculoskeletal and Skin Diseases Advisory Council and the National Advisory Council on Aging.

Review Criteria

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written review, comments on the following aspects of the application will be made in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered in the assignment of the overall score.

(1) Significance: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

(2) Approach: Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

(3) Innovation: Does the project employ novel concepts, approaches or method?
Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

(4) Investigator: Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

(5) Environment: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements?

In addition, the adequacy of plans to include both genders and minorities and their subgroups as appropriate for the scientific goals of the research will be reviewed. Plans for the recruitment and retention of subjects will also be evaluated.

The initial review group will also examine the provisions for the protection of human and animal subjects, the safety of the research environment, and conformance with the NIH Guidelines for the Inclusion of Women and Minorities as Subjects in Clinical Research.

AWARD CRITERIA

The anticipated date of award is September 30, 1998. Awards will be based upon the following criteria:

- scientific merit
- availability of funds
- programmatic priorities of the funding ICD
- responsiveness to the RFA

INQUIRIES

Written and telephone inquiries concerning this RFA are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Direct inquiries regarding programmatic issues to:

Bernadette Tyree, Ph.D.
Cartilage and Connective Tissue Program
National Institute of Arthritis and Musculoskeletal and Skin Diseases
45 Center Drive, Room 5AS-37J, MSC 6500
Bethesda, MD 20892-6500
Telephone: (301) 594-5032
FAX: (301) 480-4543
Email: tyreeb@ep.niams.nih.gov

Chhanda Dutta, Ph.D.
Geriatrics Program
National Institute on Aging
7201 Wisconsin Avenue, Suite 3E-327, MSC 9205
Bethesda, MD 20892-9205
Telephone: (301) 435-3048
FAX: (301) 402-1784

Email: duttac@exmur.nia.nih.gov

Direct inquiries regarding fiscal matters to:

Ms. Nancy Curling
Grants Management Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
45 Center Drive, Room 5AS-43B, MSC 6500
Bethesda, MD 20892-6500
Telephone: (301) 594-3503
FAX: (301) 480-4543
Email: nc23a@nih.gov

Mr. Joseph Ellis
Grants and Contracts Management Office
National Institute on Aging
7201 Wisconsin Avenue, Suite 2N212, MSC 9205
Bethesda, MD 20892-9205
Telephone: (301) 496-1472
FAX: (301) 402-3672
Email: ellisj@gw.nia.nih.gov

Schedule

Letter of Intent Receipt Date: March 15, 1998
Application Receipt Date: April 28, 1998
Initial Review: June, 1998
Second Level Review: September 1998
Anticipated Award Date: September 30, 1998

AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.846. Awards are made under authorization of the Public Health Service Act, Title IV, Part A (Public Law 78-410), as amended by Public Law 99-158, 42 USC 241 and 285) and administered under PHS grants policies and Federal Regulations 42 CFR 52 and 45 CFR Part 74. This program is not

subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, public law 103-227, the pro-children act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the America people.

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